RFP Questions Received – Updated Aug 11, 2020

Logistics, Process, and Budget

- **Is there a preferred cost-sharing percentage?** There is not a predefined or preferred cost sharing percentage dictated by ETC. As stated in the RFP, any funding provided by ETC should be considered seed funding towards the project with the collaborator investing as well.
- **Are there any limitations on what the cost-sharing can be spent on (i.e. salaries, materials, etc.)?** No, there are no limits on cost-sharing expenses other than the expenses should be related to the project.
- **Are there any limitations on what the RFP funding can be spent on (i.e. salaries, equipment, etc.)?** No, there are no limits on what the RFP funding can be spent on other than expenses should be related to the project.
- **What are the collaborating partner capabilities? Is that something we should discuss with individual collaborators or will that be decided after proposal submission? What role can the partners play (i.e. piloting, testing, developing, analyzing)?** In general, ETC members participating on this project will be available to provide Subject Matter Expertise to support the collaboration through piloting, testing, helping with development, analyzing data, providing feedback, etc. The exact details and support requests from ETC members should be included in the proposal and can be discussed in more detail as part of the proposal evaluation process. Note, typically any samples provided by ETC are non-proprietary, off the shelf samples; if a vendor requires or an ETC member wishes to provide proprietary samples for evaluation, that will be handled and discussed with the individual members as part of the project scoping process.
- **Can we envision collaboration with partners to measure heat/mass transport coefficients in relevant reaction environments, or in the development of COMSOL simulations for Residence Time Distribution?** Yes, the proposal can include collaboration with the ETC to measure or estimate reactor parameters. ETC members can conduct experimental characterization and/or support modeling (e.g. COMSOL) to determine reactor parameters such as heat/mass transport and residence time distribution
- **Is there a limitation or range to the overall allowed budget?** No, the budget for this project has not been set and will be based upon the selected proposal and the interest of ETC members to fund a given proposal.
- **Are joint proposals considered from academic institutions, or is it preferred to have a single institution lead and have a collaborator indicated from another institution?** Joint proposals from academic institutions and/or commercial organizations will be considered. However, for keeping the execution of the collaboration agreement the simplest the preference is that one institution/organization acts as the primary and have the other be a collaborator/subcontractor.
- **"Direct costs" only reduces the scope of what we can do, as our budgeting typically includes indirect overhead as we work with students and have facilities. Is there any way to include indirect costs in the budget? We can't realistically prototype a reactor without indirect costs**

and overhead. We could reduce the scope of our proposal to accommodate "direct costs" only if needed. We may be able to negotiate down indirect cost rates for industrial funding, as well. A respondent may include "Indirect costs" in their budget. If a proposal is selected, ETC may further negotiate the costs to align with available budget. Please note that "Direct Costs" in the ETC context includes items such as faculty salaries, postdoctoral and student fellowships, supplies, equipment, travel, etc. It is important that whatever budget proposed represents the final fixed cost to ETC inclusive of any indirect costs.

- **Can you let us know the funding range (ballpark) for academic work on such a project? This will help us frame the proposal scope.** As stated above, the budget will be based upon the selected proposal and the interest of ETC members to fund a given proposal. If the available budget is less than what was requested, ETC will look to negotiate the costs to align with the available budget; this negotiation could include reduction of direct costs, indirect costs or scope of the project. Respondents are encouraged to provide a budget that will satisfy the requirements and requested deliverables specified in the RFP.
- **Since the overall budget and cost-sharing is proposal specific, to justify the amount of cost-sharing with ETC, the market potential of the proposed cells/system is required. If the development is successful what level of commitment from ETC members can be expected? i.e. how many systems at the two different scales are the ETC members expected to require at the end of the project. What interest would you expect outside of the consortium?** Our antitrust guidelines prohibit ETC's members from sharing their purchasing information (i.e., pricing, commitments) with ETC so we cannot comment on this nor will ETC seek to gather this information. Furthermore, ETC will not commit to the purchase of systems by its members following the conclusion of any project. Simply stated, each of our members makes its own, with no influence or direction provided by ETC.

  With regards to interest outside the consortium, given that the projects are based upon the collective needs of the pharmaceutical community it is the goal for the technology derived from any ETC project to be broadly applicable to that community, not just those companies participating in the collaboration. Vendors are welcome to reach out to any company they wish to conduct their own market research based on the individual input that company may choose to share.

Scope of Technology

- **Should solutions be focused on recirculation of streams, or is there interested in targeting single-pass conversion for Phase I.** For Phase I, the ETC does not have a requirement on recirculation of streams vs. single-pass mode.
- **Is there specific equipment currently being used/approved in pharma that we should consider for the proposal?** Regarding the design of the electrochemical cell, ETC members have used both plate style reactors and batch/CSTR style reactors. Each style has strengths and weaknesses. There is not a specific preference for one over the other, but should meet the requirements described in the RFP. Other designs may also be suitable.
    - **Specific heating/cooling devices** - Heating/cooling is typically done with single fluid recirculation systems (e.g. recirculating chillers with silicon oil)

- **Pumps, potentiostats, power supplies – are there preferred ones used across the board? Is there an existing framework for control? Are you looking to integrate with specific equipment/inputs, or a standalone system with its own equipment/inputs?**
    - **For pumps**, we recommend allowing flexibility on the types of pumps that can be used, as companies have different preferences on pump choice. Specific pump selections do not need to be included in the design.
    - **For power supplies**, there is no preference for specific power supplies. The power supply requirement for the plant scale reactor must provide up to ~20 V and ~60-200 A. There is also an optional requirement for the power supply to allow switching polarity, as that mode may be beneficial for some reaction types. Several examples of commercially available power supplies which may satisfy the voltage/current needs of the project are summarized in the table below. This table was compiled by ETC from information found on each manufacture's website and is provided for informational purposes only. Respondents are not restricted to these examples in their proposal. It is the responsibility of the respondent select an appropriate power supply to satisfy the electrical safety and requirements for their specific reactor design.

Manufacturer	Rohde-Schwarz	ExTech	BK Precision	Volteq	TDK Lambda
Model	Model -NGP-800	382275	9152	HY5020EP	Z36-24-LAN-(L/L2)-U
Voltage Output	0-32VDC	0-30VDC	0-30VDC	0-50V	0-36V
Current Output	0-20Amps (Configurable)	0-20Amps	0-18Amps	0-20Amps	0-24Amps
Power (Watts)	Up to 800Watts (Configurable)	600Watts	540Watts	Not specified	864Watts
Communication	Yes – Internal Data Logging USB Interface	No	No	Yes - Arduino Interface USB or RS485	Yes – Drivers for Lab View & Lab Windows
Configurable	YES	NO	NO	NO	No
NRTL*	YES	NO	NO	NO	YES

**NRTL = Nationally Recognized Testing Laboratory*

    - **Regarding control**, we request standalone system and are not looking to integrate with other equipment.

- **Up to what scale is a reference electrode useful/necessary? Is this more for R&D, early development, process development, or all the way up to manufacturing scales?** Reference electrode is useful for the lab development reactor. It is requested that the initial prototype of the plant scale reactor has the ability to include reference electrode to confirm design/scale-up parameters. But the reference electrode can be phased out in later builds.
- **For automation and PLC integration - Can we work together with ETC members to understand what is already in place at different manufacturing sites? Should a PLC system be developed from scratch, or are there existing frameworks to work with? If the latter, what are the**

desired outputs of the platform to integrate with existing PLC networks? Is there any interest in the development of an Arduino-based platform to control power supplies, pumps, and heaters? Automation and PLC integration generally apply to the plant scale equipment only. A PLC system should not be developed from scratch, but would be incorporated into existing PLC systems. The PLC platforms may differ from facility to facility. The desired functions would be temperature (process and jacket) control and monitoring, process pressure monitoring, reactor valve position controls, power supply (voltage, current) controls and monitoring, and controlling any inherent safety features. For the lab development scale unit, there is interest in having simple control system that would control some aspects of the reactor (e.g. Arduino-based platform) - especially power supply information and control, temperature monitoring and control. Due to the variety of pumps used, pumps would not need to be controlled.

- **Can you be specific as to the limitation/weaknesses of currently used cells, especially at the small scale and in particular weaknesses of the commercially available micro-flow cells?** In the ETC group's experience, the limitations primarily reside around manufacturing scale reactors/cells. The issues we've identified are as follows:
    - Most current larger scale cells do not have adequate chemical compatibility in housing or gaskets.
    - Most units do not have suitable electrical equipment controls to be used in hazardous areas (e.g. Class I, Division 1 locations).
    - Units generally require a separate power supply. For safety and equipment robustness purposes, the ETC group wishes to have a dedicated power supply integrated into the unit, with appropriate electrical ratings for hazardous areas

  Based on the team's experience, the commercially available micro-flow cells support most of the requirements for lab scale unit set out in the RFP. However, importantly, there does not appear to be a direct scale-up version of these micro-flow cells – e.g., smaller scale units tend to be constructed of PTFE (which is highly chemical compatible) and larger units are made of PP or PVDF, which is not compatible with many organic solvents.

- **Why is a pressure requirement of 3 bar suggested? Are you requiring the system to be pressure rated? Are there particular reactions of interest at high pressure?** The 3 bar pressure is for example purposes only. At a minimum the unit needs to be leak proof and accommodate back pressure generated from turbulence generators or other flow restrictions, and any static head from the liquid column. Generally, in a manufacturing facility it is desired for process equipment to have some nominal pressure rating above atmospheric pressure. There is no specific plan to run reactions at elevated pressure, however in the case of gas-generating reactions, there would be benefit to operate at elevated pressures to reduce the gas volume in the reactor.

- **What are the anticipated solution volume range (min/max) for both reactors?** There isn't a target volume for the electrochemical reactor itself, since it is generally expected that the reactor will be run in a flow through mode. (The reactor could be run in single-pass mode, or in a recirculating mode with a holding tank. Either approach is acceptable for the project.) To help with reactor volume sizing, typically, reactions are run in the range of 5 to 20 L/kg substrate. The target production rates for the manufacturing scale reactor is 0.5 to 1 kg/hr, the volumetric flowrate that passes through the reactor can be calculated based on that information. Expected electrode surface area needed to achieve target throughput is ~1000 - 5000 cm^2 based on

typical current density of 0.01 to 0.1 A/cm^2. The small scale reactor is targeted to be ~50-100x lower production rates than the manufacturing scale reactor.

- **The anticipated solution volume range would have to take into account operating time - is 48 hours realistic?** Yes, targeting a 48 hr continuous run time is suitable for the unit and can be accommodated in a manufacturing facility.
- **Is the capability for unattended operation with automatic shutdown if any safety limits exceeded required?** The preference is for the ability to run the unit unattended for periods of time, with human intervention and adjustments to the unit as needed. Regarding equipment/process safety, it will be important to have automatic fail-safe features incorporated into the unit that allows a safe shutdown if safety limits are exceeded (e.g. temperature, pressure, voltage/current).